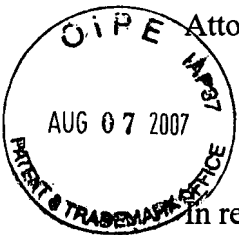


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Attorney's Docket No. 11.036011

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Cohenford, Menisha Group Art Unit: 1637  
Appl. No.: 10/730,575 Examiner: Samuel Woolwine  
Filed: December 8, 2003  
For: **A NOVEL METHOD FOR DNA AMPLIFICATION USING DNA  
BLOCKING PROBES**

**SECOND AMENDED APPEAL BRIEF**

Sir:

This Second Amended Appeal Brief is filed in response to the "Notice of Non Compliance" mailed July 19, 2007 and pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed October 16, 2006.

**Real Party in Interest.**

The real party in interest in this appeal is Cytoc Corporation, Inc., the assignee of the above-referenced patent application.

**Related Appeals and Interferences.**

There are no related appeals and/or interferences involving this application or its subject matter.

**Status of Claims.**

Claims 3-16 and 18 are the subject of this appeal. The claims appear in Appendix A. No other claims are pending. Claims 1-2, 17, and 19-23 have been cancelled.

### **Status of Amendments.**

In the Advisory Action dated February 2, 2005, the Examiner indicated that the Amendment After Final filed July 10, 2006 was entered. Thus, all of Appellant's amendments have been entered.

### **Summary of Claimed Subject Matter.**

The pending claims of the present invention are directed to a process for the amplification of a DNA template by subjecting a sample of biological material containing a target nucleotide sequence to amplification using a non-extendable oligonucleotide blocker. A summary of the independent claims is presented below:

Claim 3: A method for amplifying a target nucleic acid sequence comprising the steps of; forming a nucleotide amplification reaction mixture (see page 3, paragraph [0032]) comprising a DNA template containing a target nucleic acid sequence (see page 3, paragraph [0028]; also Figure 1 "DNA"); a single chimeric oligonucleotide primer consisting of a deoxyribonucleotide sequence with a ribonucleotide base at the 3' terminus that binds to said DNA template (see page 2, paragraphs [0025] and [0028]; also Figure 1 "Chimeric Primer"); a non-extendable oligonucleotide blocker that binds to said DNA template downstream from said primer (see page 3, paragraph [0019]; also Figure 1 "DNA Blocker"); a DNA polymerase which lacks 5' exonuclease activity; and a double-strand-specific ribonuclease (see page 2, paragraphs [0022] to [0023]), and appropriate buffers and nucleic acid precursors; subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a first primer extension product is formed and cleaved at the ribonucleotide base releasing said first primer extension product (see page 2, paragraphs [0018] and [0032]; also Figure 1 "Extension Product"); hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer

extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base (see page 3, paragraph [0034]; also Figure 1 "DTT A"); subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a target amplification product is formed and said first DNA triggering template is cleaved at the ribonucleotide base releasing said second primer sequence with a ribonucleotide base at the 3' terminus; hybridizing said second primer sequence to a second DNA triggering template which contains a second primer sequence binding site at the 3' terminus (see page 4, paragraph [0035]; also Figure 1 "DTT-B"); and subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a third primer extension product is formed and cleaved at the ribonucleotide base releasing said third primer extension product, wherein said third primer extension product has the same nucleotide sequence as the first primer extension product (see page 4, paragraph [0035]).

Claim 10: A method for amplifying a target nucleic acid sequence comprising the steps of; forming a nucleotide amplification reaction mixture (see page 3, paragraph [0032]) comprising a DNA template(see page 3, paragraph [0028]; also Figure 1 "DNA"); a single chimeric oligonucleotide primer consisting of a deoxyribonucleotide sequence with a ribonucleotide base at the 3' terminus that binds to said DNA template (see page 2, paragraphs [0025] and [0028]; also Figure 1 "Chimeric Primer"); a non-extendable oligonucleotide blocker that binds to said DNA template downstream from said primer (see page 3, paragraph [0019]; also Figure 1 "DNA Blocker"); a DNA polymerase which lacks 5' exonuclease and strand displacement activity (see page 2, paragraphs [0022] to [0023]); a double-strand-specific ribonuclease; and appropriate buffers and nucleic acid precursors; subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a first primer extension product is formed and cleaved at the ribonucleotide base releasing said first

primer extension product (see page 2, paragraph [0016]); hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base (see page 3, paragraph [0034]; also Figure 1 "DTT A");

subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a target amplification product is formed and said first DNA triggering template is cleaved at the ribonucleotide base releasing said second primer sequence with a ribonucleotide base at the 3' terminus; hybridizing said second primer sequence to a second DNA triggering template which contains a second primer sequence binding site at the 3' terminus (see page 4, paragraph [0035]; also Figure 1 "DTT-B"); subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a third primer extension product is formed and cleaved at the ribonucleotide base releasing said third primer extension product, wherein said third primer extension product has the same nucleotide sequence as the first primer extension product (see page 4, paragraph [0035]); repeating steps c)-f); and detecting amplification of said target sequence.

#### **Grounds of Rejection to be Reviewed on Appeal.**

Whether claims 3-16 and 18 are patentable under 35 U.S.C. § 103(a) over Richards (U.S. Patent No. 5,645,987) in view of U.S. Patent No. 6,251,639 to Kurn and in further view of U.S. Patent No. 5,916,777 to Kacian.

## **ARGUMENT**

***Issue-- Whether claims 3-16 and 18 are patentable under 35 U.S.C. § 103(a) over Richards (U.S. Patent No. 5,645,987) in view of U.S. Patent No. 6,251,639 to Kurn and in further view of U.S. Patent No. 5,916,777 to Kacian.***

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or combined references) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Appellant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

**I. The prior art references of Richards (USP 5,645,987), Kurn (USP 6,251,639 ) and Kacian (USP 5,916,777) either alone or in combination, do not teach or suggest all the claim limitations of claims 3-16 and 18.**

In the Non-Final Office Action of January 5, 2006 regarding the rejection under 35 U.S.C. § 103(a) as it applied to claims 3 and 10 and maintained in the Final Office Action of July 10, 2006, the examiner stated that:

“It would have been *prima facie* obvious to one of skill in the art at the time that the time the invention of the instant application was made to incorporate the chimeric primers and RNase H digestion taught by Kacian and the ‘blocker’ oligonucleotides taught by Kurn in the ‘primer extension cascade’ taught by Richards.”

The Appellant respectfully disagrees.

The Appellant submits that Richards neither anticipates the claims nor are they made obvious by either Kurn or Kacian. The Examiner responded to the Appellant's argument by stating that one cannot show non-obviousness by attacking references individually where the

rejections are based on combinations of references. Although the Appellant agrees that one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references, the Appellant also would point out that the Examiner, in order to establish *prima facie* obviousness of a claim, must demonstrate that all of the limitations of the claim must be taught or suggested by the prior art. In re Royka 490 F.2d 981 (CCPA 1974). Therefore, if the Appellant can demonstrate that all the limitations of the present claims cannot be found in Richards alone or in combination with Kurn or Kacian, then the Examiner has not established *prima facie* obviousness.

Richards does not teach or suggest all of the limitations of the claims of the present invention. In the Office Action of January 5, 2006, the Examiner argues that Richards teaches a method comprising a primer extension cascade in which the cleaved and released primer extension product from a first primer extension reaction serves as a primer in a subsequent primer extension reactions (as depicted in Figure 6). The Examiner points out the claim limitations that Richards does not teach such as a chimeric primer, blocking oligonucleotides, thermocycling, RNase to digest the primer extension products or the use of a DNA polymerase which lacks 5' exonuclease activity. The Appellant has argued (in Appellant's response of August 18, 2006) that the Examiner missed at least one very important additional limitation in the method of the present invention that is not taught in Richards, Kurn or Kacian. In particular, the Appellant points to section (c) which is identical in both independent claims 3 and 10. Section (c) reads as follows:

- c.) hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base; (emphasis added)

As described in Claims 3 and 10 as well as demonstrated in Figure 1 of the Appellant's application, the method of the present invention is a multi step process which results in the amplification of a target sequence (or triggering template). Unlike the process described in

Richards, the method of the present invention does not cleave oligonucleotides from extension products using restriction enzymes which are then used for future rounds of amplification. As described in the claims, the second primer extension product formed by the extension of the first primer extension product is cleaved at the ribonucleotide base at the 5' end of the first DNA triggering template. Thus, the second primer extension product is formed by the cleavage by RNase H at a ribonucleotide base at the 5' end of the target sequence, not the primer extension product as shown in Richards. In the Advisory Action dated September 15, 2006, the Examiner argues that Richards teaches this limitation in Figure 6 except for the presence of a ribonucleotide base joining the "second primer sequence" to the 5' end of the target sequence. The Appellant would argue that this is a very important distinction. The method of the present invention teaches the binding of a first extension product binding to a target sequence which has an extension product binding site and a ribonucleotide base at the 5' end of the target sequence which, when cleaved by RNase H, creates a second primer sequence. Nothing in Richards nor Kurn or Kacian teaches or suggests a method which utilizes these components. Although Richards does not teach or suggest the release of a second primer sequence from the target sequence, the Examiner argues that Kacian teaches an equivalent means of releasing a primer extension product by incorporating a ribonucleotide base at the 3' end of the primer to provide a substrate for RNase H. The Appellant respectfully disagrees. It seems that the Examiner is arguing that although Richards does not teach the release of a second primer sequence from the target sequence, since Kacian teaches the release of a primer extension product through the cleavage of a ribonucleotide base at the 3' end of a nucleotide sequence, any method that uses RNase H cleavage of any primer sequence must be obvious. Obviously, such is not the standard for establishing *prima facie* obviousness. As mentioned previously, to establish *prima facie* obviousness the prior art reference (or combined references) must teach or suggest all the claim limitations. In the present case, the Examiner has clearly not established that Richards, Kurn or Kacian either alone or in combination teach or suggest a contiguous second primer sequence which is conjoined to the 5' end of a target sequence by a ribonucleotide base. Thus, a *prima facie* case obviousness has not been established by the Examiner.

Also, in the Office Action of July 10, 2006, the Appellant called attention to the fact that the two DNA triggering templates used in the method of the present invention are distinct from the original DNA sequence from which the first extension product is created. The Examiner has not pointed to any teaching or suggestion in Richards, Kurn or Kacian either alone or in combination where two distinct templates that are different in composition than the original DNA template which generates the first primer extension product are used in an amplification process. In the Advisory Action of September 15, 2006, the Examiner argues that such a limitation is not found in the claim. The Appellant respectfully disagrees. As mentioned previously, claims 3 and 10 in subsection (c), describe a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base which comprises the first DNA Triggering Template (see DTT A in Figure 1). The original DNA template which binds the DNA blocker is a naturally occurring nucleotide which contains no such ribonucleotide base. The second DNA triggering template, as described in claims 3 and 10 in subsection (e), contains a second primer sequence binding site at the 3' terminus. Thus, the original DNA template must be structurally different than the two DNA triggering templates which, in turn, are different in composition from each other. Because Richards does not recite the use of two DNA triggering templates in addition to the original DNA template, it does not contain all the limitations of the claimed invention.

Combining the Richards patent with the Kurn patent and the Kacian patent cannot make up for the deficiencies mentioned above in regards to the Richards patent with respect to the presented claimed invention. Neither the Kurn patent or the Kacian patent teach or suggest a method for amplifying DNA by the use of two DNA triggering templates. Thus, a *prima facie* case obviousness has not been established by the Examiner.

Lastly, the Appellant would point out that the claims of the present invention describe the creation of a second primer sequence, through RNase H cleavage, which contains a ribonucleotide base at the 3' terminus (claims 3 and 10 subsection (d)). The creation of this second primer sequence with a ribonucleotide base at the 3' terminus is important because the second primer sequence binds to a second DNA triggering template (DTT-B) which is then



extended and cleaved at the ribonucleotide base thus creating a third primer extension product that has the same nucleotide sequence as the first primer extension product. The Examiner has not pointed to any teaching in Richards, Kurn or Kacian where a primer extension product is created that contains a ribonucleotide base at the 3' terminus. Thus, a *prima facie* case obviousness has not been established by the Examiner.

For these reasons, the rejection of claims 3-16 and 18 under 35 U.S.C. § 103(a), should be reversed.

**II. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.**

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

A new combination of elements can be patented "whether it be composed of elements all new, partly new or all old." *Rosmount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546, 221 USPQ 1, 7 (CAFC 1984). The Court of Appeals for the Federal Circuit has forcefully stated that a claim rejection must provide a specific motivation in the art for combining elements from cited art in order to establish obviousness of a new combination.

"[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. ... [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular. ... Broad conclusory statements regarding the

teaching of multiple references, standing alone, are not 'evidence.' ... [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination ... to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed. Cir. 1999), emphasis added.

*Dembiczak* involved patent claims to "a large trash bag made of orange plastic and decorated with lines and facial features, allowing the bag, when filled with trash or leaves, to resemble a Halloween-style pumpkin, or jack-o'-lantern." *Dembiczak*, 996, 1616. The prior art cited by the Board included: a book describing how to teach children to make a "Crepe Paper Jack-O-Lantern;" a book describing a method of making a "paper bag pumpkin" by stuffing a bag with newspapers, painting it orange, and then painting on facial features with black paint; a U.S. Patent describing a bag apparatus wherein the bag closure is accomplished by the use of folds or gussets in the bag material; design patents issued to *Dembiczak*; and prior art "conventional" plastic lawn or trash bags. The Federal Circuit held that the claimed pumpkin-style trash bag was not obvious because there was no clear, particular motivation to combine the cited references.

This holding of *Dembiczak* that evidence of motivation to combine must be clear and particular to establish obviousness has been emphasized over and over again by the Federal Circuit since *Dembiczak* was decided. It was strongly reemphasized in *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161 (Fed. Cir. 2000):

In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. See, e.g., *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("[T]he Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); *In re Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617 ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). "Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of

obviousness." Sibia Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000); Tec Air, Inc. v. Denso Mfg., Inc., 192 F.3d 1353, 1359, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with those of another reference).

... there is "a general rule that combination claims can consist of combinations of old elements as well as new elements," Clearstream Wastewater Sys. v. Hydro-Action, Inc., 206 F.3d 1440, 1446, 54 USPQ2d 1185, 1189-90 (Fed. Cir. 2000), "[t]he notion . . . that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1575, 1 USPQ2d 1593, 1603 (Fed. Cir. 1987); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) ("It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements."). *Ruiz* at 1167

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to compel a person of ordinary skill in the art to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. "It would have been *prima facie* obvious to one of skill in the art at the time the invention of the instant application was made to incorporate the chimeric primers and RNase H digestion taught by Kacian and the "blocker" oligonucleotides taught by Kurn in to the 'primer extension cascade' taught by Richards". (Office Action at page 6, second paragraph).

This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required under *In re Dembiczak*. The claims here are no more obvious than those at issue in *Dembiczak*. No clear, particular suggestion or motivation in the prior art to make the specific method for amplifying a target nucleic acid sequence comprising the steps of;

- a) forming a nucleotide amplification reaction mixture comprising a DNA template containing a target nucleic acid sequence; a single chimeric oligonucleotide primer consisting of a deoxyribonucleotide sequence with a ribonucleotide base at the 3' terminus that binds to said DNA template; a non-extendable oligonucleotide blocker that binds to said DNA template downstream from said primer; a DNA polymerase which lacks 5' exonuclease

activity; and a double-strand-specific ribonuclease, and appropriate buffers and nucleic acid precursors;

b) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a first primer extension product is formed and cleaved at the ribonucleotide base releasing said first primer extension product;

c) hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base;

d) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a target amplification product is formed and said first DNA triggering template is cleaved at the ribonucleotide base releasing said second primer sequence with a ribonucleotide base at the 3' terminus;

e) hybridizing said second primer sequence to a second DNA triggering template which contains a second primer sequence binding site at the 3' terminus; and

f) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a third primer extension product is formed and cleaved at the ribonucleotide base releasing said third primer extension product, wherein said third primer extension product has the same nucleotide sequence as the first primer extension product.”

as recited in both claims 3 and 10 and much less for the claims dependent thereon with their additional limitations. The obviousness rejection is based on hindsight from disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention. Withdrawal of this rejection under 35 USC 103(a) is respectfully requested.

In the Office Action of July 10, 2006, the Examiner argues that “...the “primer extension cascade” taught by Richards is so similar to the method claimed in the instant application as to render the latter obvious because the essential differences between the methods taught by Richards and those of the instant application are that Richards uses the primer extension to create

a substrate for restriction endonuclease cleavage, while the Appellant uses the primer extension to create a substrate for RNase H cleavage" (see page 6 first paragraph). The Appellant would argue that just because the methodologies are similar does not make them obvious. There are many different types of polymerase chain reaction amplification methodologies (e.g., Inverse PCR; RT-PCR; Asymmetric PCR; Quantitative PCR; Touchdown PCR; RACE-PCR; Multiplex-PCR; etc.) however, it is difficult to imagine that one of skill in the art would agree that all of these methods are obvious in light of the original discovery of the polymerase chain reaction. To argue that two methodologies are obvious because they are similar ignores the many complexities of protocols in molecular biology. Very small changes in methods can result in very dramatic changes in the outcome of those methods. In the present case, the differences between the methodology of Richards as compared to the method of the present invention are more than small changes in protocol. The use of completely different templates for amplification simply cannot be considered an insignificant difference. In fact, the Appellant would argue that using completely different templates makes the methodologies fundamentally different and unique from one another. The cleavage of the template to generate an extension primer is yet another example of one of many differences between the methodology of Richards and the methodology of the present invention. As such, *prima facie* obviousness has not been established under such conditions.

In view of the foregoing, the Appellant respectfully submits that Richards, Kurn and Kacian either alone or in combination, fail to teach or suggest the method of amplifying DNA as recited in the claims. For these reasons, the rejection of claims 3-16 and 18 under 35 U.S.C. § 103(a), should be reversed.

### **III. There is no reasonable expectation of success.**

Under section 103(a), "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in Appellant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed.Cir. 1991), quoting *In re Dow Chemical*

*Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). The Appellants believe that the Examiner has failed to establish a *prima facie* case of obviousness, since neither Richards nor Kurn or Kacian alone or in combination, fail to provide the necessary expectation of success for the ordinarily skilled artisan to arrive at the claimed invention. The references Richards, Kurn and Kacian all describe the synthesizing of oligonucleotide primers from a single molecule template. The synthesized oligonucleotides can be subsequently used as primers on the same single molecule template to generate identical primers for an amplification reaction. There would be no expectation that the components from the methods of Richards, Kurn or Kacian could function in the method of the present invention. Some of the unique features of the present invention include: 1) the use of two DNA triggering templates, 2) the creation of three extension primer products, one of which contains a ribonucleotide base at the 3' terminus, and 3) the incorporation of contiguous second primer sequence which is conjoined to the 5' end of a target sequence by a ribonucleotide base. Since neither Richards, Kurn or Kacian contemplate the use of any of the above mentioned components, it is difficult to imagine that one of skill in the art at the time the invention was made would have conceived of the method of the present invention. There can be no expectation of success if the prior art of record does not include all of the limitations of the present claims.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness, since of Richards, Kurn or Kacian alone or in combination, fail to provide the necessary expectation of success for the ordinarily skilled artisan to arrive at the claimed invention. For these reasons, the rejection of claims 3-16 and 18 under 35 U.S.C. § 103(a), should be reversed.

Applicant: Cohenford  
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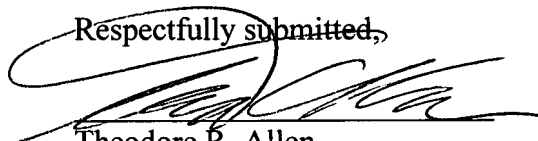
Docket No. 11.036011

### CONCLUSION

In view of the arguments presented above, the Appellants contend that each of claims 3-16 and 18 are patentable. Therefore, reversal of the rejections under 35 U.S.C. §103(a) is respectfully solicited.

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Respectfully submitted,



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## APPENDIX A: CLAIMS APPENDIX

3. A method for amplifying a target nucleic acid sequence comprising the steps of;
- a) forming a nucleotide amplification reaction mixture comprising a DNA template containing a target nucleic acid sequence; a single chimeric oligonucleotide primer consisting of a deoxyribonucleotide sequence with a ribonucleotide base at the 3' terminus that binds to said DNA template; a non-extendable oligonucleotide blocker that binds to said DNA template downstream from said primer; a DNA polymerase which lacks 5' exonuclease activity; and a double-strand-specific ribonuclease, and appropriate buffers and nucleic acid precursors;
  - b) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a first primer extension product is formed and cleaved at the ribonucleotide base releasing said first primer extension product;
  - c) hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base;
  - d) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a target amplification product is formed and said first DNA triggering template is cleaved at the ribonucleotide base releasing said second primer sequence with a ribonucleotide base at the 3' terminus;
  - e) hybridizing said second primer sequence to a second DNA triggering template which contains a second primer sequence binding site at the 3' terminus; and
  - f) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a third primer extension product is formed and cleaved at the ribonucleotide base releasing said third primer extension product, wherein said third primer extension product has the same nucleotide sequence as the first primer extension product.



4. The method of claim 3 wherein said DNA polymerase is the Stoffel1 fragment of Taq polymerase and has strand displacement activity.
5. The method of claim 3 wherein said double-strand-specific ribonuclease is thermostable RNaseH.
6. The method of claim 3 wherein said thermocycle includes a hybridization step at a temperature in the range of 30 to 50 degrees Celsius, a primer extension step at a temperature in the range of 50 to 70 degrees Celsius, and a double-strand-specific ribonuclease cleavage step at a temperature in the range of 50 to 70 degrees Celsius.
7. The method of claim 3 wherein said thermocycle is begun at a temperature in excess of 85 degrees Celsius.
8. The method of claim 3 wherein said nucleotide amplification reaction mixture is a polymerase chain reaction mixture.
9. The method of claim 3 wherein said nucleotide amplification reaction mixture includes a molar excess of said first and second DNA triggering templates over said DNA template.
10. A method for amplifying a target nucleic acid sequence comprising the steps of;
  - a) forming a nucleotide amplification reaction mixture comprising a DNA template; a single chimeric oligonucleotide primer consisting of a deoxyribonucleotide sequence with a ribonucleotide base at the 3' terminus that binds to said DNA template; a non-extendable oligonucleotide blocker that binds to said DNA template downstream from said primer; a DNA polymerase which lacks 5'

- exonuclease and strand displacement activity; a double-strand-specific ribonuclease; and appropriate buffers and nucleic acid precursors
- b) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a first primer extension product is formed and cleaved at the ribonucleotide base releasing said first primer extension product;
  - c) hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base;
  - d) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a target amplification product is formed and said first DNA triggering template is cleaved at the ribonucleotide base releasing said second primer sequence with a ribonucleotide base at the 3' terminus;
  - e) hybridizing said second primer sequence to a second DNA triggering template which contains a second primer sequence binding site at the 3' terminus;
  - f) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a third primer extension product is formed and cleaved at the ribonucleotide base releasing said third primer extension product, wherein said third primer extension product has the same nucleotide sequence as the first primer extension product;
  - g) repeating steps c)-f);and
  - h) detecting amplification of said target sequence.

11. The method of claim 10 wherein said DNA polymerase is the Stoffel1 fragment of Taq polymerase.

12. The method of claim 10 wherein said double-strand-specific ribonuclease is a thermostable RNaseH.
13. The method of claim 10 wherein said thermocycle includes a hybridization step at a temperature in the range of 30 to 50 degrees Celsius, a primer extension step at a temperature in the range of 50 to 70 degrees Celsius, and a double-strand-specific ribonuclease cleavage step at a temperature in the range of 50 to 70 degrees Celsius.
14. The method of claim 10 wherein said thermocycle is begun at a temperature in excess of 85 degrees Celsius.
15. The method of claim 10 wherein said nucleotide amplification reaction mixture is a polymerase chain reaction mixture.
16. The method of claim 10 wherein said target product in step d) is labeled with a detectable marker and said labeled target product is detected in step h).
18. The method of claim 10 wherein said nucleotide amplification reaction mixture includes a molar excess of said first and second DNA triggering templates over said DNA template.

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## **APPENDIX B: EVIDENCE**

**NONE**

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### **APPENDIX C: RELATED PROCEEDINGS**

**NONE**

**CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)**

Applicant(s): Cohenford

Docket No.

11.036011

Application No.

10/730,575

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Examiner

Samuel Woolwine

Customer No.

0000 38732

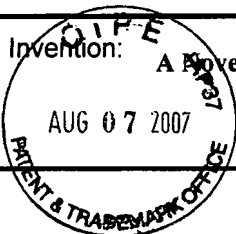
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Invention:

A Novel Method for DNA Amplification using DNA Blocking Probes

AUG 07 2007



I hereby certify that the following correspondence:

Response to Notice of Non-Compliant Appeal Brief - mailed 07-19-07

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